REMARKS

Claims 1, 2, and 4-33 are pending in the present application. Claim 3 has been cancelled without prejudice or disclaimer of the subject matter therein. Claims 1, 2, 15, and 16 have been amended in order to more distinctly define the present invention. New claims 28-33 have been added in order to further define the present invention. Support for the claim amendments can be found, *inter alia*, on pages 3 and 7 of the specification as well as in originally filed claim 3. Accordingly, no new matter has been introduced into the application by the above-amendment.

Interview Summary

Applicants wish to express their appreciation to Examiners Gollamudi and Hartley for the courtesies extended to the undersigned representative during the personal interview of January 29, 2003. During the interview, applicants pointed out that the present invention served to reduce or minimize the formation of a heretofore undisclosed impurity, namely amlodipine aspartate, in an amlodipine maleate pharmaceutical composition. By creating an acidic environment, the impurity-forming reaction is suppressed. Accordingly, claim 1 recites a pH of 5.5 to 6.8. The stability data in the instant application for samples A and X were briefly reviewed as an example of the effectiveness of the present invention. The merits of the rejections were also addressed wherein applicants pointed out the deficiencies of the applied patents to establish a *prima facie* case of obviousness. These reasons are incorporated into the remarks hereinafter.

Rejection over Davison

Claims 1-9, 11, 14-18, and 22 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303). This rejection is respectfully traversed.

No Prima Facie case of Obviousness

The Examiner has misread Davison in making the instant rejection. Specifically the Examiner asserts that Davison directs or motivates the reader to formulate compositions having a pH near that of blood, namely 7.4. This is not true. Column 2 lines 26-31 of Davison teaches that the "[amlodipine] salt which provide solutions having a pH close to that of blood (7.4) are preferred because they are readily biocompatible . . ." Thus, Davison is describing a characteristic by which a salt is selected; not a criterion for forming a solid form pharmaceutical. The pH is that of the salt, not the pharmaceutical composition.

Because of this basic factual error, the Examiner's conclusion of obviousness is likewise in error. Specifically, nothing in Davison teaches, suggests or motivates the reader to make an amlodipine maleate solid composition having a pH within the range of 5.5 to 6.8. The disclosure in column 2 on which the Examiner relies merely directs the reader to select a different amlodipine salt than amlodipine maleate; i.e., a salt having a higher pH than amlodipine maleate and thus closer to 7.4. Accordingly, the Examiner has failed to supply any motivation for adjusting the pH of the pharmaceutical composition to a pH of 5.5 to 6.8.

Moreover, the disclosure of the pH of the amlodipine salt as a selection criteria in Davison in no way suggests forming a solid form pharmaceutical having such a pH. Indeed,

unlike a solution that can be injected in to the blood stream, a solid form pharmaceutical is normally administered perorally wherein the active is released in the very acidic stomach environment. The pH of the composition has little effect on the pH of the stomach and rather, the composition is substantially modified by the pH of the stomach. Accordingly, pH is not taught or suggested in Davison to affect the bioavailability or biocompatibility of a solid form pharmaceutical.

Notwithstanding the above, even if the Examiner persists in asserting that Davison suggest obtaining a solid form pharmaceutical having a pH near 7.4, nothing in Davison suggests providing a composition having a pH of 5.5 to 6.8. Indeed, why would a worker skilled in the art, given such a teaching, select an acidic pH within the applicants' claimed range instead of an alkaline pH nearer to 7.4? Only improper hindsight reconstruction can lead to such a selection.

Finally, applicants point out that merely using calcium phosphate and sodium starch glycolate in an amlodipine maleate composition does not inherently form a pH within the applicants' claimed range, as the Examiner appears to assert in the last sentence of the rejection. Instead, the pH would depend, *inter alia*, on the type of calcium phosphate as well as the relative amounts of all the ingredients. Commercial calcium phosphates are generally considered alkaline (e.g., Di-Tab is pH 7.4). However, some brands/grades are acidic as described on page 6 of the present specification. Thus, picking which brand, etc. will affect the pH of the composition. Therefore, the applicants' claimed pH range is not inherently and necessarily formed by a composition containing calcium phosphate and sodium starch glycolate.

In summary, Davison fails to teach a solid form pharmaceutical composition having the applicants' claimed pH. Davison is in fact silent as to the pH of solid form pharmaceutical compositions. Nothing in Davison suggests any desirability in selecting the applicants' claimed pH range. In the absence of some motivation to modify Davison in order to obtain an amlodipine maleate composition having a pH within the range of 5.5 to 6.8, the Examiner has failed to establish a *prima facie* case of obviousness and withdrawal of the rejection on this basis alone is required.

Secondary Considerations

Considering the invention as a whole further evidences the patentability and unobviousness of the present invention. Amlodipine maleate was initially the preferred salt for the development of a pharmaceutical, but was replaced with the besylate salt because of tabletting and stability problems. (See the FDA FOIA material, of record, and Davison column 1 lines 25-26.). The present inventors have discovered a solution to the stability problems. In particular, the formation of amlodipine aspartate is suppressed by providing an acidic pH. This is because the aspartate derivative is formed by a Michael addition reaction between amlodipine and maleic acid and a Michael addition generally requires an alkaline environment. Nothing suggests that a pH within the range of 5.5 to 6.8 could address the stability problems associated with amlodipine maleate.

That the present invention provides this unexpected advantage is demonstrated by the data in the present specification. For example, sample A has a pH of 6.13 while sample X has

a pH of 8.68. (See specification pages 10 and 13, respectively). Example 5 shows that amlodipine aspartate (i.e., Z#204) grows in one month under 40°C/75%RH in sample A from 0.16 to 0.24 while in sample X it grows from 0.13 to 1.73 (See specification pages 14 and 16, respectively). This demonstrates and confirms the principle of the present invention whereby controlling the pH to a specified acidic range can improve stability. Nothing in Davison suggests a stability improvement by controlling pH. The advantages of the presently claimed invention are thus unexpected and unobvious. The other inventive samples produce similar superior results (see, e.g. samples B-F).

During the interview, the Examiner criticized the data as not comparing the closest prior art. However, the pH of 7.4 mentioned in Davison does not refer to the pH of a solid form pharmaceutical composition and thus 7.4 is not a prior art composition. Indeed, no precise amlodipine maleate composition is disclosed in Davison. Accordingly, the data is not properly criticized on this basis as applicants do not have to create prior art for making a comparison and the comparison in the present specification is sufficient to show the unobviousness of selecting the applicants' claimed pH range.

Therefore, the formation of the presently claimed invention, including its advantages, could not have been obvious from Davison at the time that the invention was made. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection over Davison in view of EP 0089167

Claims 12 and 13 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of EP 0089167. This rejection is respectfully traversed.

Specifically, the present rejection is in error for at least the reasons set forth above with regard to Davison. Inasmuch as Davison is insufficient to render claim 1 unpatentable and EP 0089167 is not asserted to overcome these deficiencies, the instant rejection of dependent claims 12 and 13 is likewise improper. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection over Davison in view of Sherwood

Claims 10, 19 and 20 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of Sherwood et al. (US 5585115). This rejection is respectfully traversed.

Specifically, the present rejection is in error for at least the reasons set forth above with regard to Davison. Inasmuch as Davison is insufficient to render claim 1 unpatentable and Sherwood is not asserted to overcome these deficiencies, the instant rejection of dependent claims 10, 19 and 20 is likewise improper. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection over Davison in view of Sherwood and further in view of Schobel

Claim 21 has been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of Sherwood et al. (US 5585115) and further in view of Schobel (US 4687662). This rejection is respectfully traversed.

Specifically, the present rejection is in error for at least the reasons set forth above with regard to Davison. Inasmuch as Davison in deficient to render claim 1 unpatentable and Sherwood and Schobel are not asserted to overcome these deficiencies, the instant rejection of dependent claim 21 is likewise improper. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection over Davison in view of Schobel

Claims 23-27 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of Schobel (US 4687662). This rejection is respectfully traversed.

The Examiner has misunderstood the teaching of Schobel. Specifically, Schobel teaches a granulate containing a therapeutic agent to have a particle size of 100 to 600 microns. In contrast, claim 23 recites that the active itself, namely amlodipine maleate, have a specified particle size. Schobel does not speak to the issue of the particle size of the therapeutic active. Thus, Schobel does not teach or suggest the applicants' claimed average particle size of amlodipine maleate. Therefore, Schobel does not provide any motivation to form the

applicants' claimed invention from the general teachings of Davison. In the absence of such motivation the rejection is improper and reconsideration and withdrawal of this rejection are requested.

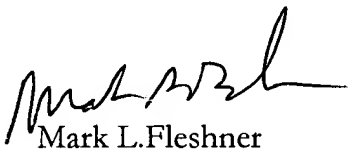
CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the application is in condition for allowance. Favorable consideration and prompt allowance are earnestly solicited.

If the Examiner believes that any additional changes would place the application in better condition for allowance, the Examiner is invited to contact the undersigned attorney, Mark R. Buscher, at the telephone number listed below.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this, concurrent and future replies, including extension of time fees, to Deposit Account 16-0607 and please credit any excess fees to such deposit account.

Respectfully submitted,
FLESHNER & KIM, LLP



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